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ORIGINAL ARTICLE

Clinical Profile and its Associations with Coronary Angiography Results in a Public University Hospital

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Abstract

Background: Ischemic heart disease is one of the most common causes of death worldwide. There are few data in the literature about the association of clinical profile and coronary angiography results in the Brazilian population.

Objectives: To assess clinical variables and their associations with the results of coronary angiography and to evaluate the safety of coronary angiography in a public university hospital.

Methods: From August 2015 to April 2018, 1844 patients submitted to coronary angiography at the Pedro Ernesto University Hospital (HUPE, acronym in Portuguese) were enrolled in this cross-sectional study. They were evaluated by their clinical variables, angiographic results, and procedure complications. Logistic regression was used, and the criterion for determining significance was set at 5%.

Results: The median age was 62 years, and most of the population (71%) were outpatients. Stable angina was the most common indication (62.9%). Only 19.7% underwent noninvasive cardiac testing. Arterial hypertension was the most prevalent (88.2%), followed by dyslipidemia (60.2%). Most patients (65%) had obstructive coronary artery disease (CAD). Left main coronary artery (LMCA) stenosis was found in 8.1% of patients. Older age, male sex, quantity of risk factors (RF), and peripheral artery disease were risk predictors for CAD. Death occurred only in 0.16% of the population, and acute coronary artery occlusion in 0.2%.

Conclusion: Classic RF showed an association with CAD. The low incidence of complications suggests that coronary angiography is a safe procedure to be conducted in a public university hospital.

Keywords: Coronary Artery Disease; Risk Factors; Coronary Angiography.

Introduction

Cardiovascular diseases, principally ischemic heart disease and stroke, are the leading cause of global mortality.[1] The main cause of ischemic heart disease is coronary artery disease (CAD). The Framingham Heart Study[2] and its cohorts defined the risk factors (RF) for CAD, changing the way preventive medicine is currently applied. The growth of the population and the prevalence of associated CAD makes it essential to identify patients at high risk for the occurrence of cardiac events.

Coronary angiography is the gold standard exam for assessing coronary anatomy and diagnosing CAD.[3] The incidence of complications related to the method is less than 1%.[4] The risk of adverse events for each patient depends on a variety of factors including the following: demographic characteristics, cardiovascular anatomy, clinical condition, comorbidities, practitioner experience, and the type of procedure involved. The increased availability of catheterization laboratories in Brazil has made coronary angiography more accessible to patients who suffer from CAD. This procedure is available in all major cities of Brazil, and it is provided by the Brazilian Unified Health System (SUS).

There is very little data in the Brazilian medical literature regarding the results of coronary

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Central Illustration: Independent predictors of obstructive CAD and LMCA stenosis

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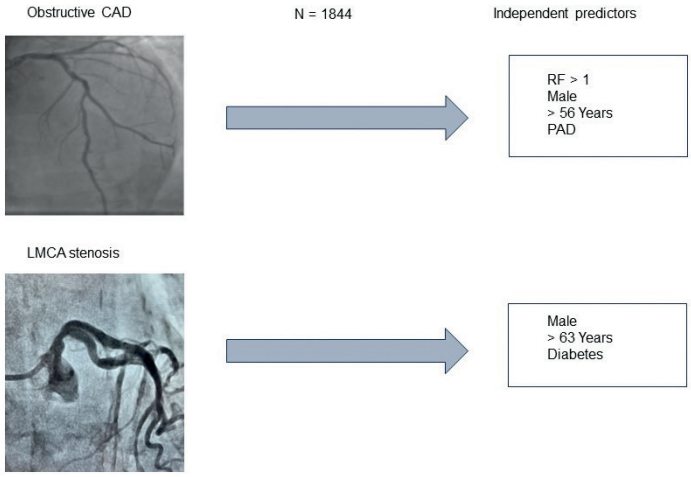

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LMCA: left main coronary artery; CAD: coronary artery disease; RF: risk factor; PAD: peripheral artery disease. Source: The autor, 2019.

angiography. Moreover, such literature sheds a bit of light on the question of how safe this invasive procedure is when administered in a public university hospital.

This article aims to assess the clinical profile and its associations with the results of coronary angiography and to evaluate the safety of coronary angiography in a public university hospital.

Methods

Study design

This is an epidemiological, observational, retrospective, and cross-sectional study, using data from patients who underwent coronary angiography at the Interventional Cardiology Service at the Pedro Ernesto University Hospital, of the State University of Rio de Janeiro (HUPE/UERJ, acronym in Portuguese), between August 2015 and April 2018.

The study was approved by the HUPE/UERJ Research Ethics Committee under number 2,087,628, CAAE 67955517.3.0000.5259 on 17 October 2018.

Target population

The study included 1,844 patients of both sexes, from SUS, HUPE/UERJ, and the State Regulation System (Sistema Estadual de Regulação, abbreviated SER in Portuguese), who underwent diagnostic coronary angiography for suspected CAD.

Data were collected from SUS nursing forms. Furthermore, the authors conducted anamnesis, analyzed the previously performed exams, and reviewed the patient's medical records.

Coronary angiography

The diagnostic procedure was performed after arterial access puncture (radial, ulnar, or femoral), usually using 5F introducer sheaths and administration of 5,000 IU of unfractionated heparin. Pre-molded or moldable diagnostic catheters were used for selective injections into the coronary arteries with non-ionic contrast medium for angiographic definition of coronary anatomy. Coronary angiography was performed by a total of 12 physicians, including specialists and residents under supervision.

Results of coronary angiography were considered as obstructive CAD when stenoses greater than 50% of arterial lumen were found in any main epicardial artery or branches, or stenosis greater than 30% in the left main coronary artery (LMCA), as recommended by the American Heart Association and American College of Cardiology (AHA/ACC).[5] Approximately 40% to 50% of moderate coronary stenosis causes myocardial

ischemia;[6,7] therefore, this study used this classification for obstructive CAD. Severe stenoses were considered when stenosis was greater than 70% in any main epicardial artery or branches, or greater than 50% in the LMCA.

Statistical analysis

Descriptive analysis of the data was performed, presented in the form of tables and expressed by mean ± standard deviation or median and interquartile range according to data normality for the continuous variables, and frequency (n) and percentage (%) for categorical data. The Shapiro-Wilk test was used to verify the normality of the data. Continuous variables were compared using the non-parametric Mann-Whitney test, and categorical variables were compared using the chi-square test.

In order to assess the influence of clinical variables with the presence of obstructive CAD in coronary angiography, binary logistic regression was used.

In the multivariate analysis, which identified the independent predictors for the binary outcomes, binary logistic regression was applied with the stepwise forward selection method of the variables. For multinomial outcomes, ordinal logistic regression was applied with the backward stepwise method.

The criterion for determining significance was set at 5%. The statistical analysis was processed using the statistical software SAS® System, version 6. The presence (dichotomous data) or the increases (numerical data) of the explanatory variable are related to the highest degrees of impairment.

Results

Baseline characteristics

The median age was 62 (interquartile range: 55 to 69 years), and most patients were male (57%). The origin of the indication was made through the SER in 84.5% of the cases. The most prevalent comorbidities were hypertension (88.2%), dyslipidemia (60.2%), and diabetes (32.9%). Only 19.7% of the samples underwent some type of non-invasive cardiac test. The vast majority of the population had at least 1 RF (95.8%), and patients with 3 or more RF represented 43.4% of the population (Table 1).

Stable angina was the main reason why patients were referred for coronary angiography, corresponding to 1159 (62.9%) patients (Figure 1). The majority of the participants were outpatients (71%).

Table 1 – Baseline characteristics

Variable		n (%)
Ethnicity	White	1228 (66.6)
	Brown	336 (18.2)
	Black	279 (15.1)
Sex	Male	1051 (57)
	Female	793 (43)
Origin	HUPE	285 (15.5)
	SER	1559 (84.5)
Obesity		485 (26.3)
AH		1627 (88.2)
DM		606 (32.9)
IDDM		96 (5.2)
DLP		1110 (60.2)
FH		236 (12.8)
Smoking		280 (15.2)
PAD		48 (2.6)
CKD		120 (6.5)
NIT		363 (19.7)
RF		1767 (95.8)
Number of RF	0	77 (4.2)
	1	390 (21.1)
	2	577 (31.3)
	≥3	800 (43.4)
		Median (IQR)
Age (years)		62 (55 - 69)
BMI (kg/m^2)		26.7 (24.1 - 30.1)

AH: arterial hypertension; BMI: body mass index; CKD: chronic kidney disease; DLP: dyslipidemia; DM: diabetes mellitus; FH: family history; HUPE: Pedro Ernesto University Hospital; IDDM: insulin-dependent diabetes mellitus; IQR: interquartile range; NIT: non-invasive cardiac test; PAD: peripheral artery disease; RF: risk factor; SER: State Regulation System. Source: The author, 2019.

Results of coronary angiography and characteristics of the procedure

Only 22.8% of patients were suspected of having acute coronary syndrome. Of these, 80.7% had obstructive

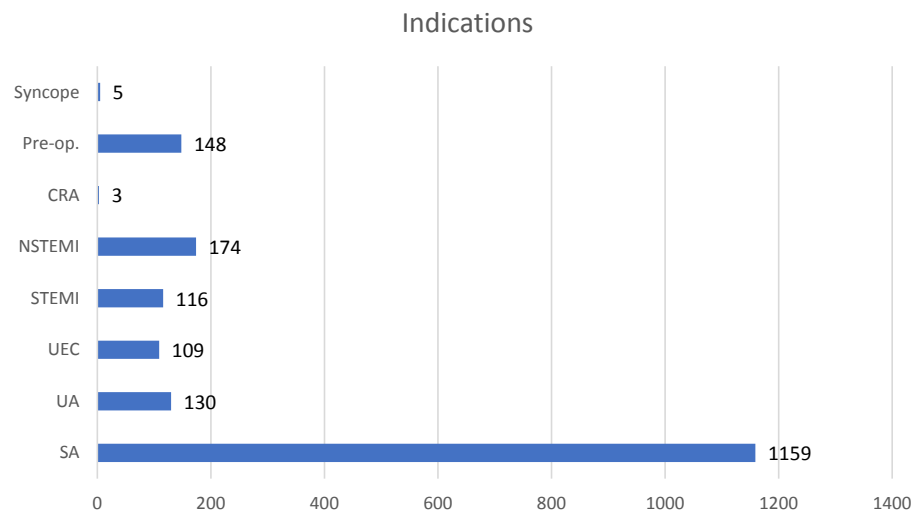

Figure 1 – Coronary angiogram indications.
CRA: cardiorespiratory arrest; NSTEMI: non-ST elevation myocardial infarction; pre-op: pre-operative evaluation; SA: stable angina; STEMI: ST-elevation myocardial infarction; UA: unstable angina; UEC: undefined etiology cardiomyopathy. Source: The author, 2019.

CAD. Stable patients (77.2%) were diagnosed with obstructive CAD in 60.3% of cases (Figure 2).

The most widely used arterial access route was radial in 91.7% of cases. Most of the studied patients (65.0%) had obstructive CAD, with 381 of them (20.7%) classified as single-vessel disease, 336 (18.2%) as double-vessel disease, and 482 (26.1%) as triple-vessel disease. The most frequently affected vessels were the anterior descending artery with 824 lesions, the right coronary artery with 772 lesions, and the circumflex artery with 498 lesions. LMCA stenosis was diagnosed in 150 (8.1%) cases, and severe stenosis was more frequent, in 87 (4.7%) cases. When considering only obstructive CAD with severe stenosis, 58.2% of the population was diagnosed: 384 (20.8%) being classified as single-vessel disease, 292 (15.8%) as double-vessel disease, and 397 (21.6%) as triple-vessel disease.

Regarding the complications of the procedure, death occurred in 3 (0.16%) patients, acute coronary artery occlusion in 4 (0.2%), and anaphylaxis (or anaphylactoid reaction) in 2 (0.1%) patients. There were no neurological events, major bleeding (drop in hemoglobin > 3 g/dl, blood transfusion, or vascular surgery), acute lung edema, or need for surgical vascular correction. All procedures were performed by residents with staff physician supervision.

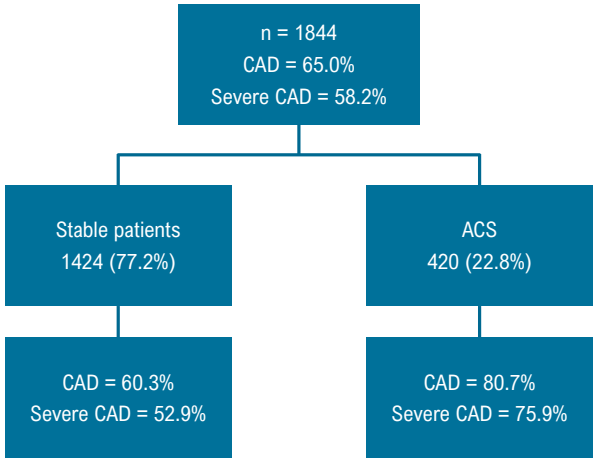

Figure 2 – Prevalence of CAD in stable and acute coronary syndrome patients.
ACS: acute coronary syndrome; CAD: coronary artery disease. Source: The author, 2019.

Association of clinical variables with CAD

The following clinical variables showed significant associations ($p < 0.05$) with obstructive CAD: older age, male sex, hypertension, diabetes, dyslipidemia, family history of CAD, smoking, peripheral arterial disease, and number of RF (Table 2).

Table 2 – Obstructive CAD and clinical variables

Variables		Obstructive CAD		p value	OR	95% CI
		Yes (1199) n (%)	No (645) n (%)			
Age group (years)	≤55	242 (20.2)	229 (35.5)	Reference		
	56 - 62	315 (26.3)	163 (25.3)	<0.001	1.83	1.41 – 2.38
	63 - 69	326 (27.2)	135 (20.9)	<0.001	2.29	1.74 – 2.99
	≥70	316 (26.3)	118 (18.3)	<0.001	2.53	1.92 – 3.35
Male sex		748 (62.4)	303 (47.0)	<0.001	1.87	1.54 – 2.27
Obesity		282 (23.5)	203 (31.5)	0.18	0.83	0.63 – 1.09
AH		1094 (91.2)	533 (82.6)	<0.001	2.19	1.65 – 2.91
DM		472 (39.4)	134 (20.8)	<0.001	2.48	1.98 – 3.09
NIDDM		394 (32.9)	116 (18.0)	<0.001	2.38	1.88 – 3.02
IDDM		73 (6.1)	23 (3.6)	<0.021	1.75	1.09 – 2.83
DLP		815 (68.0)	295 (45.7)	<0.001	2.52	2.07 – 3.07
FH		170 (14.2)	66 (10.2)	0.016	1.45	1.07 – 1.96
Smoking		208 (17.3)	72 (11.2)	<0.001	1.67	1.25 – 2.23
PAD		46 (3.8)	2 (0.3)	<0.001	12.8	3.10 – 53.0
CKD		91 (7.6)	29 (4.5)	0.011	1.74	1.14 – 2.68
1 RF		171 (14.3)	219 (34.0)	<0.001	2.76	1.55 – 4.90
2 RF		368 (30.7)	209 (32.4)	<0.001	6.21	3.53 – 10.9
≥3 RF		643 (53.6)	157 (24.3)	<0.001	14.5	8.21 – 25.5
NIT		221 (18.4)	142 (22.0)	0.07	0.80	0.63 – 1.01

AH: arterial hypertension; CAD: coronary artery disease; CI: confidence interval; CKD: chronic kidney disease; DLP: dyslipidemia; DM: diabetes mellitus; FH: family history; IDDM: insulin-dependent diabetes mellitus; NIDDM: non-insulin-dependent diabetes mellitus; NIT: non-invasive cardiac test; OR: odds ratio; PAD: peripheral artery disease; RF: risk factor. Significant values for p < 0.05, according to binary logistic regression. Source: The author, 2019.

The following clinical variables showed significant associations ($p < 0.05$) with LMCA stenoses: older age, male sex, diabetes mellitus, and number of RF ≥ 3 (Table 3).

The results of the multivariate analysis (Table 4) showed that the number of RF, male sex, the age group above 56 years old, and peripheral arterial disease were considered independent predictors for obstructive CAD. The following were independent predictors for LMCA stenoses: male sex, age > 63 years, and diabetes (Table 5).

Discussion

In this study, the comparison of the clinical profile with the results of coronary angiography is relevant for the identification of the clinical characteristics that are associated with CAD in the population of patients treated at a public university hospital.

It is difficult to compare these results with those produced in other studies because of the differing inclusion criteria. However, this study included a comprehensive consideration of the definition of CAD; therefore, the comparison based on the presence of obstructive CAD was not impaired, despite the difference in definitions used in other studies. Limited data were found for comparison of LMCA stenosis in the literature. In Chart 1, the main clinical variables and the presence of CAD in the studied population are described together with the results of contemporary studies that also

Table 3 – LMCA stenosis and clinical variables

Variables		LMCA stenosis		p value	OR	95% CI
		Yes (150) n (%)	No (1 694) n (%)			
Age group (years)	≤55	20 (13.3)	451 (26.6)		Reference	
	56 – 62	35 (23.3)	443 (26.2)	0.045	1.78	1.01 – 3.13
	63 – 69	43 (28.7)	418 (24.7)	0.002	2.32	1.34 – 4.01
	≥70	52 (34.7)	382 (22.6)	<0.001	3.07	1.80 – 5.23
Male sex		108 (72.0)	943 (55.7)	<0.001	2.05	1.42 – 2.96
Obesity		32 (21.3)	453 (26.7)	0.19	0.73	0.46 – 1.17
AH		136 (90.7)	1491 (88.0)	0.34	1.32	0.75 – 2.34
DM		61 (40.7)	545 (32.2)	0.034	1.44	1.03 – 2.03
NIDDM		54 (36.0)	456 (26.9)	0.014	1.55	1.10 – 2.21
IDDM		7 (4.7)	89 (5.3)	0.76	0.88	0.40 – 1.94
DLP		98 (65.3)	1012 (59.7)	0.18	1.27	0.89 – 1.80
FH		24 (16.0)	212 (12.5)	0.22	1.33	0.84 – 2.11
Smoking		29 (19.3)	251 (14.8)	0.14	1.38	0.90 – 2.11
PAD		5 (3.3)	43 (2.5)	0.56	1.32	0.52 – 3.39
CKD		12 (8.0)	108 (6.4)	0.44	1.28	0.69 – 2.38
1 RF		18 (12.0)	372 (22.0)	0.43	1.81	0.41 – 7.99
2 RF		48 (32.0)	529 (31.2)	0.094	3.40	0.81 – 14.3
≥3 RF		82 (54.7)	718 (42.4)	0.045	4.28	1.03 – 17.8
NIT		33 (22.0)	330 (19.5)	0.46	1.17	0.78 – 1.75

AH: arterial hypertension; CI: confidence interval; CKD: chronic kidney disease; DLP: dyslipidemia; DM: diabetes mellitus; FH: family history; IDDM: insulin-dependent diabetes mellitus; LMCA: left main coronary artery; NIDDM: non-insulin-dependent diabetes mellitus; NIT: non-invasive cardiac test; OR: odds ratio; PAD: peripheral artery disease; RF: risk factor. Significant values for p < 0.05, according to binary logistic regression. Source: The author, 2019.

evaluated clinical characteristics, RF and CAD in patients undergoing coronary angiography.

Obstructive CAD in the studied population was detected in 65.0% of cases and 58.2% of patients had severe stenosis. These figures are below the values estimated (73% to 80%) by the ACC.[8] The study conducted by Patel et al.[9] provided a comprehensive examination of CAD in patients who underwent coronary angiography. In this study, over 1,989,779 exams of the National Cardiovascular Data Registry (NCDR) were conducted between January 2004 and April 2008. The researchers found a prevalence of severe CAD in 60.3% of the sample population, but only 37.6% in patients who were suspected of having stable CAD. In cases of prevalence of CAD above moderate degrees of stenoses, the percentage in stable patients rose to 41%. The present study showed a similar result in the prevalence of CAD in the sample population, but a higher prevalence among patients with suspected stable CAD (Figure 2).

Costa Filho et al.[10] published a study examining 830 patients with suspected stable CAD referred for elective coronary angiography. In their sample, 27.8% of patients had CAD with severe stenosis; when considering CAD above moderate degree of stenosis, the prevalence rose to 32.2%. That study included only stable patients and also excluded patients who were previously diagnosed with CAD; those differences in method design might explain our study's higher prevalence of obstructive CAD.

Table 4 – Multivariate analysis: logistic regression for obstructive CAD

Number	Model variable	p value	OR	95% CI
1	Number of RF	<0.001		
	1 RF	0.003	2.42	1.34 – 4.37
	2 RF	<0.001	5.63	3.14 – 10.1
	≥3 RF	<0.001	13.2	7.35 – 23.7
2	Male sex	<0.001	1.96	1.58 – 2.43
3	Age group (years)	<0.001		
	≤ 55	0.007	Reference	
	56 – 62	<0.001	1.48	1.11 – 1.98
	63 – 69	<0.001	1.86	1.38 – 2.50
	≥70	<0.001	2.21	1.62 – 3.01
4	PAD	0.010	6.64	1.57 – 28.1

CAD: coronary artery disease; CI: confidence interval; OR: odds ratio; PAD: peripheral artery disease; RF: risk factor. Source: The author, 2019.

Table 5 – Multivariate analysis: logistic regression for LMCA stenosis

Number	Model variable	p value	OR	95% CI
1	Male sex	<0.001	2.08	1.44 – 3.02
2	Age group (years)	<0.001		
	≤ 55	Reference		
	56 – 62	0.075	1.67	0.95 – 2.95
	63 – 69	0.003	2.25	1.30 – 3.90
	≥ 70	<0.001	2.95	1.73 – 5.05
3	NIDDM	0.026	1.50	1.05 – 2.14

CI: confidence interval; LMCA: left main coronary artery; NIDDM: non-insulin-dependent diabetes mellitus; OR: odds ratio. Source: The author, 2019.

The multivariate analysis indicated that male sex and older age were independent risk predictors for CAD and LMCA stenosis. Additionally, it is evident there is an increase in proportional risk with age for all the analyzed outcomes, as well as the result found by Patel et al.[9] that demonstrated an increment in odds ratio of 1.29 in each succeeding age cohort of 5 years older (95% confidence interval: 1.28 to 1.30).

As expected, all classical RF showed a statistically significant association with CAD. The number of RF has been highly correlated with CAD outcomes, as shown in Table 4. A study published in Jordan has shown that the patients who underwent coronary angiography had at least 1 RF.[11]

Many studies do not consider peripheral arterial disease as a RF for CAD,[12,13] but recent studies have "contradicted" that notion.[14-19] The REACH Registry has conducted a multicenter study for 3 years involving 67,888 patients.[20,21] There was an incidence of 14.8% of acute myocardial infarction, brain stroke, and death in patients diagnosed with peripheral arterial disease, greater than the one found in the group of patients who had suffered from only CAD (11.6%). In this study, only 48 (2.6%) patients had this comorbidity, a prevalence similar to that of the population of another Brazilian study.[10] This variable proved to be an independent risk predictor for obstructive CAD, as shown in the multivariate analysis. These data highlight the importance of this condition, which often goes unnoticed in the clinical examination.

Only 19.7% of patients underwent any non-invasive test for ischemia before coronary angiography, and the most frequent method was the cardiac stress test (61%). This rate is below those obtained in other populations (64.8% and 88.9%) examined in similar studies.[10,22] Other studies have shown that non-invasive tests for ischemia were a risk predictor for CAD.[9,10]

Only a small number of patients who underwent coronary angiography suffered from serious complications. This is a notable result in light of the fact that this study was conducted at a public university hospital, focused on resident training. The findings of this study are consistent with those discovered in other studies.[4] Even though the number of complications is very low, the statistics of mortality presented a significant difference when compared to another recent study with 43,786 coronary angiography procedures and only 0.011% mortality.[23] The highest rate of this complication in the current sample might be related to the fact that this service is a training center; however, we would need more concrete studies to evaluate this. Deaths were caused by acute LMCA occlusion in 1 case and in 2 patients presenting cardiogenic shock referred for emergency coronary angiography.

Chart 1 – Contemporary studies on CAD

	Present study	Al-Shudifat et al., 2017[11]	Costa Filho et al., 2015[10]	Ferreira et al., 2012[22]	Galon et al., 2010[28]	Patel et al., 2010[9]
n	1844	557	830	207	1282	397954
Age (years) (IQR)	62 (55 – 69)	55	61	58.5 (mean)	65.4 (mean)	61galon
BMI (kg/m^2) (IQR)	27.4±5.0 (24.1 – 30.1)	-	27,8	-	-	29.6
Male sex (%)	57.0	70.9	49.0	58.9	53.7	52.7
AH (%)	88.2	47.4	81.0	71.5	79.6	69.6
DM (%)	32.9	38.6	35.5	22.2	31.6	26.0
DLP (%)	60.2	5.7	66.6	45.4	43.4	62.5
FH (%)	12.8	35.7	-	-	30.0	30.0
Smoking (%)	15.2	51.5	16.5	35.8	17.5	32.1
PAD (%)	2.6	-	2.8	-	-	7.0
CKD (%)	6.5	-	-	-	13.2	-
NIT (%)	19.7	-	64.8	41.6	-	83.9
CAD (%)	65.0	63.9	32.2	64.7	72.7	41.0
Severe CAD(%)	58.2	-	23.8	62.3	-	37.6
LMCA stenosis (%)	8.1	-	-	-	2.3	-
Severe LMCA stenosis (%)	4.7	-	5.6	1.9	-	3.9

AH: arterial hypertension; BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; DLP: dyslipidemia; DM: diabetes mellitus; FH: family history; IQR: interquartile range; LMCA: left main coronary artery; NIT: non-invasive cardiac test; PAD: peripheral artery disease. Source: The author, 2019.

The low incidence of complications can be related to the high number of stable patients (77.2%), as well as the fact that most procedures were performed via radial access (91.7%). As previously demonstrated by Jolly et al.[24] only 1.2 % of vascular complications in the group were due to radial access, compared to 3.0% in the femoral access group ($p < 0.001$). Romagnoli et al.[25] demonstrated a lower mortality index in the group of patients with ST-elevation myocardial infarction (STEMI) who underwent the procedure via radial versus femoral access (5.2% versus 9.2%; $p = 0.02$). The reduced number of procedures via femoral artery access made vascular surgery unnecessary in all the cases. Furthermore, surgical intervention for vascular complications is very rare when the procedure is performed through the radial artery;[26] on the other hand, when the procedure is performed via femoral access, the occurrence of complications, such as arteriovenous fistula, pseudoaneurysm, and retroperitoneal hematoma increase the frequency of surgical approach to up to 1.6%.[27] Regarding the rate of neurological events, this complication did not occur in the present series, differing from another recent study that presented a rate of neurological events of 0.056%.[23]

This study has limitations. As this is an observational cross-sectional study, the determination of causality is not achievable; in addition, variables with low prevalence require very large samples for better statistical analysis. Also, because it is a single-center study, carried out in a tertiary hospital dedicated to teaching in the state of Rio de Janeiro, questions may arise regarding the external validity of the results.

Access to medical records and characteristics of patients referred via the SER were limited several times. In these cases, clinical data were characterized through a brief anamnesis before the procedure.

Despite the limitations, the availability of an organized database led to a satisfactory numerical result. Furthermore, these findings will contribute to the improvement of HUPE's interventional cardiology service. In light of the discoveries of the present study, it is possible to improve the specialization for training interventionists and the quality of patient care. Moreover, these findings can encourage other medical practitioners to expand their data on this subject. By virtue of the quantitative contributions of this study, other medical practitioners will be able to refine their numerical figures and generate multicenter analyses with greater statistical robustness.

Conclusions

Classic RF showed an association with CAD. Advanced age, male sex, high number of RF, patient referral by HUPE, and peripheral arterial disease were considered predictors of risk for CAD. The low incidence of complications suggests that coronary angiography is a safe procedure to be conducted in a public university hospital.

Author Contributions

Conception and design of the research and critical revision of the manuscript for intellectual content: Costa GBF, Albuquerque DC; acquisition of data and statistical analysis: Costa GBF, Ferreira E; analysis and interpretation of the data: Costa GBF; writing of the manuscript: Albuquerque DC

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee on Animal Experiments of the Comitê de Ética e Pesquisa HUPE/UERJ under the protocol number 2.967.216 / CAEE: 67955517.3.0000.5259.

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